A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ISIS 304801 Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Published: 20-08-2014
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Primary objective: To evaluate the efficacy of ISIS 304801 (300 mg once weekly) as compared to placebo on the percent change in fasting triglycerides (TG) from baselineSecondary objective: To evaluate the efficacy of ISIS 304801 (300 mg once weekly...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON42059

Source
ToetsingOnline

Brief title
ISIS 304801-CS6 / Approach Study

Condition

- Lipid metabolism disorders

Synonym
Familial Chylomicronemia Syndrome (FCS)

Research involving
Human

Sponsors and support

Primary sponsor: ISIS Pharmaceuticals
Source(s) of monetary or material Support: Isis Pharmaceuticals

Intervention

Keyword: apoC-III, Chylomicronemia Syndrome (FCS), Familial, ISIS 304801

Outcome measures

Primary outcome

The primary endpoint is the % change in fasting TG from baseline as measured at the primary analysis time point.

Secondary outcome

The secondary endpoints include:

• Postprandial TG change from baseline

• Absolute change from baseline in fasting TG as measured at the primary analysis time point

• Treatment response rate, where a patient with fasting plasma TG <750 mg/dL at the primary analysis time point is defined as a responder

• Treatment response rate, where a patient who achieves >=40% reduction in fasting TG from baseline at the primary analysis time point is defined as a responder

• Frequency and severity of patient reported abdominal pain during the treatment period

• Composite of episodes of acute pancreatitis and patient reported abdominal pain during the treatment period

• Change from baseline in hepatosplenomegaly as assessed by MRI

Study description

Background summary

ISIS 304801 is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3* untranslated region of the apoC-III mRNA and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 304801 to the cognate mRNA results in the RNase H-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisensemediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target
protein levels.

Study objective

Primary objective: To evaluate the efficacy of ISIS 304801 (300 mg once weekly) as compared to placebo on the percent change in fasting triglycerides (TG) from baseline

Secondary objective: To evaluate the efficacy of ISIS 304801 (300 mg once weekly) as compared to placebo on the:
• Postprandial TG change from baseline
• Absolute change from baseline in fasting TG
• Proportion of patients who achieve fasting TG <750 mg/dL
• Proportion of patients who achieve >=40% reduction from baseline in fasting TG
• Patient reported abdominal pain
o Frequency
o Severity
• Composite of episodes of acute pancreatitis and patient reported abdominal pain
• Change from baseline in hepatosplenomegaly as assessed by MRI

Tertiary/Exploratory Objective: To evaluate the effect of ISIS 304801 (300 mg once weekly) as compared to placebo on:
• Percent change from baseline in fasting apoB-48 and chylomicron-TG
• Postprandial apoB-48 and chylomicron-TG change from baseline
• Percent change from baseline in fasting apolipoprotein C-III (total apoC-III, HDL-apoC-III, and very low density lipoprotein-apoC-III [VLDL-apoC-III])
• Other fasting lipid measurements, including: non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C
• Lipoprotein particle size/number
• Quality of Life questionnaires (EQ-5D, SF-36)

• Other symptoms: eruptive xanthoma, lipemia retinalis
• Post heparin lipoprotein lipase mass and activity
• Postprandial glucose, insulin and C-peptide (may be evaluated in patients with T2DM)
• Adjudicated acute pancreatitis event rate prior to first dose of study drug (including events based on medical chart review) vs. treatment emergent events.

Safety Objectives:
• To evaluate the safety and tolerability of ISIS 304801
• To evaluate the effects of ISIS 304801 as compared to placebo on prospectively adjudicated acute pancreatitis events (Atlanta classification) and Major Adverse Cardiovascular Events (MACE)

Study design

This is a multi-center, randomized, double-blind, placebo-controlled study. At screening, eligible patients will enter a >= 6 week diet stabilization period. Following stabilization approximately 70 eligible patients will be randomized 1:1 to receive ISIS 304801 or placebo for 52 weeks. Randomization will be stratified by (1) prior history of pancreatitis, and (2) receiving concurrent fibrate and/or prescription omega-3 fatty acid. All patients will receive ISIS 304801 300 mg once per week or matching volume of placebo. Dietary counseling will commence at the start of the diet stabilization period and will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients may elect to enroll in an open-label extension (OLE) study pending study approval by the IRB/IEC and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13 week post-treatment evaluation period. The primary endpoint for the study will be evaluated after the last patient has completed the Week 52/ET visit and will be based on the percent change from baseline in fasting TG at the primary analysis time point (Month 3).

Intervention

Eligible patients will be randomized 1:1 (ISIS 304801:placebo) to receive for 52 weeks ISIS 304801 or placebo. All patients receive 1x per week ISIS 304801 300 mg or a corresponding volume of placebo

Study burden and risks

Risks: possible side effects of the medication and study procedures

Belasting: a minimum of 14 visits to the investigator; at each visit a blood sample is taken. A urine sample is taken at almost every visit (only not at weeks 12,25, 32, 44 en 51). At almost every visit the vital signs are checked

(only not at weeks 12, 25 and 51).

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age >= 18 years at time of informed consent
3. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement >= 880 mg/dL (10 mmol/L)
4. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least one of the following:
a. Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-

function mutations in Type 1-causing genes (such as LPL, apoCII, GPIHBP1, or LMF1)
b. Post heparin plasma LPL activity of <= 20% of normal
5. Fasting TG >= 750 mg/dL (8.4 mmol/L) at Screening. If the fasting TG < 750 mg/dL up to two additional tests may be performed in order to qualify.
6. History of pancreatitis (defined as a documented diagnosis of acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made). Patients without a documented history of pancreatitis are also eligible but their enrollment will be capped at 28% (i.e., <= 14 of the 50 planned patients).
7. Willing to follow a diet comprising <= 20g fat per day during the study
8. Satisfy one of the following:
a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females <= 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration
b. Males: Surgically sterile, abstinent or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

Exclusion criteria

1. Diabetes mellitus with any of the following:
a. Newly diagnosed within 12 weeks of screening
b. HbA1c >= 9.0% at screening
c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin])
d. Anticipated need to change dose or type of medication during the treatment period of the Study [with the exception of ± 10 units of insulin]
e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to screening
4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening
5. Any of the following laboratory values at Screening
a. Hepatic:
• Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert*s syndrome in which case total bilirubin must be <= 3 mg/dL
• ALT > 2.0 x ULN

• AST > 2.0 x ULN
b. Renal:
• Persistently positive (2 out of 3 consecutive tests >= 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
• Persistently positive (2 out of 3 consecutive tests >= trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing <= 5 red blood cells per high power field
• Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min
c. Cardiac Troponin I > ULN at Screening
d. LDL-C > 130 mg/dL at Screening
e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion
6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within one month of screening, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period
f. Glybera gene therapy within 2 years prior to screening
g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period
i. Plasma apheresis within 4 weeks prior to screening or planned during the study

j. Prior exposure to ISIS 304801
k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator*s discretion)
15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-07-2015
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO

Date:	20-08-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	11-12-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2016
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002421-35-NL
CCMO	NL49948.000.14

Study results

Date completed: 27-01-2017

Actual enrolment: 4